Applicant : Wely B. Floriano, Nagarajan Vaidehi,   Attorney's Docket No.: 06618-607002 / CIT 3192-C
William A. Goddard, III
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Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1.   (Currently amended) A computer implemented method for modeling ligand-protein binding interactions, comprising:

providing to a computer processor structural information describing the structure of a protein and each ligand in a set of one or more ligands;

using the structural information for the protein to identify a binding region of the protein;

identifying a plurality of preferred binding conformations for each ligand in the set of ligands in the binding region, the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a coarse-grained docking algorithm and ranking initial conformations for each ligand in the set of ligands at the binding region using docking techniques energy scoring;

optimizing the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects;

calculating a binding energy for each ligand in the set of ligands in the corresponding optimized preferred binding conformations; and

selecting for each ligand in the set of ligands the lowest calculated binding energy in the optimized preferred binding conformations, and outputting the selected calculated binding energies as the predicted binding energies for the predicted binding conformations of the set of ligands.

2.   (Previously presented) The method of claim 1, wherein:
the binding region is a known binding region defined by the structural information.

3.   (Previously presented) The method of claim 1, wherein:

the binding region is an unknown binding region; and

using the structural information for the protein to identify a binding region of the protein comprises predicting a probable binding region based at least in part on the structural information.

4.   (Currently amended) The method of claim 3, wherein using the structural information to identify a binding region of the protein comprises:

mapping the empty volumes available for ligand binding in the protein to identify one or more potential binding regions;

generating initial conformations for one or more ligands known to bind the protein using a coarse-grained docking algorithm ~~docking techniques~~ in each of the one or more potential binding regions and scoring a ~~preliminary~~ energy function for ~~at least some of~~ the initial conformations;

selecting from the initial conformations for each of the known ligands a plurality of best conformations in each of the potential binding regions based at least in part on the preliminary energy scores; and

identifying the probable binding site based on a spatial location of the best conformations.

5.   (Currently amended) The method of claim 4, further comprising:

optimizing the selected best conformations to obtain a set of energy-minimized conformations for each of the known ligands in each of the potential binding regions and scoring ~~a second preliminary~~ an energy function for each of the best conformations;

wherein identifying the probable binding site is based on a spatial location of the best conformations having the lowest ~~second preliminary~~ energy scores.

6.   (Currently amended) The method of claim 4, further comprising:

before scoring the ~~preliminary~~ energy function for each of the best conformations, calculating for each of the best conformations a percentage of the ligand surface area buried within the protein for the conformation;

wherein the ~~preliminary~~ energy function is scored only for a subset of the best conformations, wherein each of the best conformations in the subset has a calculated percentage of the ligand surface area buried within the protein which exceeds a predetermined threshold.

7.   (Cancelled)

8.   (Previously presented) The method of claim 1, wherein:

identifying a plurality of preferred binding conformations includes optimizing the selected best conformations to obtain a set of energy-minimized conformations for each of the ligands;

wherein the preferred binding conformations comprise the energy-minimized conformations.

9.   (Previously presented) The method of claim 1, wherein:
the annealing molecular dynamics includes a full atom force field.

10.   (Previously presented) The method of claim 1, wherein:
the solvation effects include a continuum description of solvation.

11.   (Previously presented) The method of claim 1, wherein:
the solvation effects include a surface-area based solvation model.

12.   (Previously presented) The method of claim 1, wherein:
calculating a binding energy for each ligand in the set of ligands includes taking the difference in the ligand energy in the protein and in solution.

13.   (Previously presented) The method of claim 1, wherein:

the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the ligand in water from the energy of the ligand in the protein.

14.   (Previously presented) The method of claim 1, wherein:

the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein.

15.   (Previously presented) The method of claim 1, further comprising:

identifying from the set of ligands one or more ligands predicted to have high binding affinity based on the calculated binding energy of the ligands in the binding site.

16.   (Previously presented) The method of claim 1, wherein:

the protein is a globular protein or a transmembrane protein.

17.-28. (Cancelled)

29.   (Previously presented) A computational model of a ligand-protein complex for a protein having an unknown binding site, the model comprising:

a computer-readable memory storing data describing an optimized preferred binding conformation for the protein and a ligand known to bind to the protein, the optimized binding conformation being generated according to the method of claim 1.

30.   (Cancelled)

31. (Currently amended) A computer program product on a computer-readable medium for modeling ligand-protein binding interactions, the computer program product comprising instructions operable to cause a programmable processor to:

provide structural information describing the structure of a protein and each ligand in a set of one or more ligands;

use the structural information for the protein to identify a binding region of the protein;

identifying a plurality of preferred binding conformations for each ligand in the set of ligands in the binding region, the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a coarse-grained docking algorithm and ranking initial conformations for each ligand in the set of ligands at the binding region using ~~docking techniques~~ energy scoring;

optimize the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects;

calculate a binding energy for each ligand in the set of ligands in the corresponding optimized preferred binding conformations;

select for each ligand in the set of ligands the lowest calculated binding energy in the optimized preferred binding conformations, and output the selected calculated binding energies as the predicted binding energies for the predicted binding conformations for each of the set of ligands.

32.-35. (Cancelled)

36. (Currently amended) The computer program product of claim 31, wherein instructions to use the structural information to identify a binding region of the protein comprises instructions to:

map the empty volumes available for ligand binding in the protein to identify one or more potential binding regions;

generate initial conformations for one or more ligands known to bind the protein using docking techniques in each of the one or more potential binding regions and scoring a ~~preliminary~~ an energy function for ~~at least some of~~ the intial conformations;

select from the initial conformations for each of the known ligands a plurality of best conformations in each of the potential binding regions based at least in part on the preliminary energy scores; and

identify the probable binding site based on a spatial location of the best conformations.

37.   (Previously presented) The computer program product of claim 31, wherein: the annealing molecular dynamics includes a full atom force field.

38.   (Previously presented) The computer program product of claim 31, wherein: the solvation effects include a continuum description of solvation.

39.   (Previously presented) The computer program product of claim 31, wherein: the solvation effects include a surface-area based solvation model.

40.   (Previously presented) The computer program product of claim 31, wherein instructions to calculate a binding energy for ligand in the set of ligands includes taking the difference in the ligand energy in the protein and in solution.

41.   (Previously presented) The computer program product of claim 31, wherein: the binding energy is calculated for a ligand according to a scoring function comprising substracting the free energy of the ligand in water from the energy of the ligand in the protein.

42.   (Previously presented) The computer program product of claim 31, wherein:

the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein.

43.   (Previously presented) The computer program product of claim 31, further comprising instructions to:

identify from the set of ligands one or more ligands predicted to have high binding affinity based on the calculated binding energy of the ligands in the binding site.

44.   (Previously presented) The computer program product of claim 31, wherein:

generating and ranking initial conformations includes scoring an energy function for at least some of the initial conformations and ranking the initial conformations based at least in part on the energy scores.

45.   (Previously presented) The computer program product of claim 31, wherein:

generating and ranking initial conformations includes determining a percentage of the ligand surface area buried within the protein for each of the initial conformations and determining energy scores only for a subset of the preferred conformations, wherein each of the preferred conformations in the subset has a calculated percentage of the ligand surface area buried within the protein which exceeds a predetermined threshold.